REMARKS

The application stand with claims 1-4, 6, 8-9, 12, 15-18 and 20-28. Claims 1, 3 and 4 are amended herein for the reasons explained below.

As a preliminary matter, Applicants submit that the amendment to the claims merely clarifies features in such a way that no new search is required. For example, the Examiner already performed searches for untranslatable forms of the PFP gene such as antisense or complimentary forms as recited in earlier versions of the claims. No new issues for search are presented. Thus, Applicants respectfully and kindly request that the Examiner enter this amendment without the filing of an RCE.

Claim 7 stands rejected under 37 CFR §1.821 for not including a sequence identifier. In response, this rejection is now moot since claim 7 was cancelled in the last Amendment of November 25, 2002. Thus, withdrawal of this rejection is respectfully requested.

Claims 1-4, 6, 8-9, 12, 15, 17-18 and 20-28 stand rejected under 35 U.S.C. §112, 1st paragraph, for lacking a written description conveying the inventor's possession of the invention as claimed. Specifically, the Examiner appears to assert that the specification does not show enough detail and/or enough nucleotide sequences (i.e. portions and fragments of the PFP gene and/or the SEQ. ID Nos. 1 and 2) to fully support the broad genus of "isolated sequences set forth in the claims."

In response, Applicants amended claims 1, 3 and 4 as recited above to remove any confusion and to clarify which portions Applicants are claiming. Specifically, as related to claim 1 for example, it is clarified that it is the introduction of an untranslatable form of either the PFP gene or a portion of the PFP gene that is used to regulate the activity of the PFP enzyme.

In an earlier Amendment of November 25, 2002, the Applicants asserted that, *inter alia*, the invention is the discovery that sucrose can be controlled by controlling the PFP enzymes by transformation. It was asserted that the written description is satisfied since methods for transformation of nucleotide sequences such as using an untranslatable form of an antisense nucleotide sequence or a complimentary sequence are known, and since the Application discloses the actual cDNA for SEQ. ID 1 and 2. The Eli Lilly case cited by the Examiner is different because in that case the actual cDNA was not disclosed (cDNA being complement DNA, as opposed to genomic or synthetic DNA). In contrast, the present case complementary DNA refers to the matching base of the disclosed cDNA.

The Examiner still maintains his position and asserts certain points Applicants now respond to in turn:

(1) The Examiner asserts that since it is not explained where in the sequence a translation initiation codon should be eliminated or where in the sequence an in-frame termination codon should be introduced, functional proteins may still be translated from one of the claimed variants. In response, Applicants submit that the odds of accidentally inserting an untranslatable sequence such that it produces functional protein translation with a sequence directly next to it is so remote that it is safe to say that it is impossible. Thus, no need exists to provide further information on determining the location for placement of the sequence to one skilled in the art other than what has been disclosed already. It is understood by one skilled in the art that insertion of the claimed sequences will not produce translation of functional proteins.

(2) The Examiner asserts that untranslatable forms of SEQ ID 1 or 2 would comprise the antisense version since it is known that antisense in "almost all cases" is not capable of translation of a functional peptide. It is not clear what the Examiner's point is here. However, it

may have stemmed from some confusion from a formality in claim 3. Claim 3 has been amended to remove any confusion that an antisense form is one type of untranslatable form as the Examiner appears to agree here.

(3) The Examiner asserts that an untranslatable form of SEQ. ID 1 or 2 reads on promoters and other regulatory sequences when considering the possible permutations. In response, claim 1 was amended to recite an untranslatable form of either the PFP gene or a portion of the gene, which eliminates promoters and other such regulators.

Finally, Applicants also submit that the specification as it exists satisfies the written description requirement and shows that the Applicants have "possession" of the claimed features because Applicants already disclosed a few examples of untranslatable forms and other species are easy to obtain by those skilled in the art. The written description is fulfilled by showing a representative number of species, and one species may be enough to satisfy this. See MPEP 2163 II.A.3.(a)(ii) (2100-164 and 2100-165, MPEP 8th ed.). Just as reciting the function of a class of compounds is enough to satisfy the written description in the *in re Herschler case* cited by the MPEP, here too, citing a few examples of untranslatable sequences and the function of those examples (e.g. for down regulating the activity of the PFP enzyme in sugarcane) is enough for one skilled in the art to "recognize that the Applicant is in possession of the necessary common attributes or features of the elements possessed by members of the genus in view of the species disclosed." *Id.*

Here the "art" is the making of an untranslatable sequence when the gene/cDNA are already known, which are circumstances that provide much more predictability in forming an untranslatable sequence than the cases cited by the Examiner where the cDNA is not known. When the art is predictable, as here, it is easy for one skilled in the art to make other species

without undue experimentation. Thus, this is the type of case where even though only a few species are disclosed, Applicants did indeed have possession of the claimed genus. The evidence that determining further species is known in the art is discussed further below for the enablement rejection. For all of these reasons, Applicants respectfully request that the rejection of claims 1-4, 6, 8-9, 12, 15, 17-18 and 20-28 under 35 U.S.C. §112, 1st paragraph, for lack of written description be withdrawn.

Claims 1-4, 6, 8-9, 12, 15, 17-18 and 20-28 under 35 U.S.C. §112, 1st paragraph, for lacking an enabling disclosure. Specifically, the Examiner asserts that sequences, such as the claimed portions (as recited in claims 3 and 6 for example), are not enabled other than the specific SEQ ID 1 and 2 sequences.

In response, the portions of the sequences as recited in the claims are enabled by the current specification because they are easily obtained by one skilled in the art without undue experimentation. The fact that some experimentation is necessary is not the test. The test is whether the experimentation is undue, and it does not matter that the experimentation may be complex. MPEP 2164.01 (citations omitted). Furthermore, not everything necessary to practice the invention need be disclosed. In fact, what is well known is best omitted.2164.08 (*citing In re Buchner*). Here, the Examiner has the duty to weigh the *In re Land* factors as explained below to determine if the specification is fully enabling.

The specification discloses down regulation, for example, based on homology dependent gene silencing in transgenic plants. As the name suggests, it is based on homology between the transgene that is used and the endogenous target sequence, and involves the interruption of the flow of information from DNA to protein (i.e. gene expression). The inventors are not aware of

any other methods by which PFP activity can be manipulated specifically, for example by chemicals or the like as it appears the examiner suggests is possible.

As one skilled in the art knows, Transgene mediated silencing depends on the identification and silencing of a target sequence by the plant based on the expression of a homologous transgene, which induces (or triggers) silencing of the target sequence. This principle that homologous sequences can induce gene silencing specifically can be achieved by various methods. More specifically, the transgene trigger can be inserted in various untranslatable forms, i.e. antisense or double stranded RNA (iRNA) to name a few untranslatable examples, as long as it is homologous to at least part of the target (endogenous) sequence.

Additionally, the whole sequence is not needed to induce silencing. Even if a partial sequence is used, it is still homologous to the target gene. The partial sequence will still target the specific part of the endogenous gene for degradation, which will render the whole transcript useless, resulting in silencing.

For example, when choosing a trigger sequence, a person skilled in the art would know they could use either a complete gene fragment, or could decide to divide the gene into two parts and use each part independently. Thus, three sequences in total could be used to silence the same gene, without the skilled person having to conduct any undue experimentation to determine these three sequences. Although these three sequences may induce silencing at different efficiencies, they will nevertheless induce silencing.

One skilled in the art also understands that homology between the gene sequences of different species also exists, so if the induction or gene silencing is homology dependent, it follows that genes from other species will also be effective.

If a protein or enzyme consists of more then one peptide or gene product, any one of the genes can be targeted and the protein or enzyme will be down regulated. PFP, for example, consists of 2 peptides, and the inventors demonstrated that the down regulation of one peptide resulted in decreased activity of the enzyme. One skilled in the art understands that the reduction of the other peptide will also lead to the same or a similar result (catalytic activity has never been shown in only one of the subunits for plant PFPs).

Furthermore, all untranslatable sequences are recognized as aberrant and are targeted for degradation. However, the mechanisms which degrade the sequences cannot distinguish between the transgene and the endogenous one, because they are homologous, with the result that both sequences are degraded. Hence, there is a decrease in the translation of the sequences, resulting in less protein and decreased activity.

Any person who is skilled in the art of genetic engineering will know which sequences are untranslatable and which are not without performing undue experimentation. For example, if a sequence of RNA does not produce any protein, then that RNA is untranslatable. Alternatively, the translation of a known sequence can be simulated using one of many known computer programs available to determine if the sequence is untranslatable or not. This is an operation which is of a simple, routine nature, and would not be regarded as undue experimentation.

Literally thousands of references are available which describe gene silencing techniques using untranslatable sequences, and some of these are listed below (copy enclosed) to show that undue experimentation would not be required by a person skilled in the art to perform the invention.

The Examiner is required to weigh the *In re Land* factors (MPEP 2164.01(a)) to determine if the specification is enabling for the full scope of the claims or not. Many of the factors weigh heavily in favor of enabling. For example, these references show that the level of one skilled in the art is very high, that finding an untranslatable sequence is very predictable to one skilled in the art, that the specification does indeed provide enough guidance for one skilled in the art (i.e. naming the gene and/or providing specific SEQ. ID sequences to build off of), and that relatively minimal experimentation is needed to find a successful untranslatable sequence portion as claimed. The references are as follows:

References

A. "(Trans) Gene Silencing in Plants: How many Mechanisms?"; Fagard and Vauoheret; Annu Rev. Plant Physiol. Plant Mol. Biol.; 2000; 51:167-94. This paper describes the various methods for gene silencing, for example using sense, antisense or double stranded forms of RNA, and other methods (see abstract).

B. "Listening to the Silent Genes: Transgene Silencing, Gene Regulation and Pathogen Control", Kooter et al.; Trends in Plant Science, Reviews; 1999, Volume 4 No. 9; p342, 347. This paper describes homology-dependent gene silencing (Abstract).

C. "RNA-Based Silencing Strategies in Plants";, Matzke et al.; Current Opinion in Genetics & Development; 2001; 11:221-227. This paper describes the use of double-stranded RNA in homology dependent gene silencing in plants.

D. "Transcriptional Gene Silencing in Plants: Targets, Inducers and Regulators"; Vaucheret and Fagara; Trends in Genetics; Vol. 17; No. 1; 2001; 29-35. This paper describes genes silencing in plants.

E. "Role of Short RNAs in Gene Silencing"; Waterhouse et al.; Trends in Plant Science; Vol 6 No. 7; 2001, 297-301. This paper describes post-transcriptional gene silencing in plants by means of non-translatable RNAs which are double-stranded or single-stranded molecules having homology to dsRNA present in the cell.

F. "Post-Transcriptional Gene Silencing in Plants"; Vaucheret et al.; Journal of Cell Science: 114; 3083-3091. This paper describes post-transcriptional gene silencing in plants.

G. "Post-Transcriptional Gene Silencing in Transgenic Sugarcane. Dissection of Homology-Dependent Virus Resistance in a Monocot that has a Complex Polyploid Genome"; Plant Physiol.; 1999April; 119(4): 1187-1198. This paper describes post-transcriptional genes silencing in sugarcane.

H. "Transgenic Plant Virus Resistance Mediated by Untranslatable Sense RNAs: Expression, Regulation, and Fate of Nonessential RNAs"; The Plant Cell; Vol. 6, Issue 10; 1441-1453. This paper describes the introduction of an untranslatable sequence which down regulates the activity of a virus (Abstract).

For all of the reasons mentioned above, Applicants submit that the enablement rejection of claims -4, 6, 8-9, 12, 15, 17-18 and 20-28 under 35 U.S.C. §112, 1st paragraph has been overcome, and respectfully request that the rejection be withdrawn.

Claims 5, 15 and 16 stand rejected under 35 U.S.C. §112, 1st paragraph for not being enabled because the relevant vectors are not available for the commissioner and the public upon issuance of a patent. In response, attached hereto is an affidavit stating that the required biological material has been deposited at the South African Sugar Association since February 1, 2000, where it is available to the commissioner presently, and will be held available for the public for the required number of years upon issuance of the patent. Since the affidavit vectors

are now available as required by the Examiner and meet the requirements of 37 CFR §1.801-§1.809, Applicants respectfully request that the §112, 1st paragraph rejection of claims 5, 15 and 16 be withdrawn. Applicants also amended the specification as recited above to provide the required notice under 37 CFR §1.809.

For all of these reasons, Applicants respectfully request reconsideration and allowance of all pending claims. The Examiner is invited to contact the undersigned attorney to expedite prosecution.

Respectfully submitted,

Joel H Bootzin
Reg. No. 42,343

Piper Rudnick
P.O. Box 64807
Chicago, IL 60664-0807
Phone: (312) 368-4000
Fax: (312) 236-7516

August 14, 2003